

(19)



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(11)

EP 1 177 729 A2

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:

06.02.2002 Bulletin 2002/06

(51) Int Cl.7: **A23L 1/30**

(21) Application number: **01306414.2**

(22) Date of filing: **26.07.2001**

(84) Designated Contracting States:

**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**

Designated Extension States:

AL LT LV MK RO SI

(30) Priority: **03.08.2000 CL 20002187**

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(54) **Pharmaceutical and food compositions containing "wood alcohols" or "wood sterols" useful for lowering serum cholesterol**

(57) Dietary utilization of mixtures containing fatty alcohols of less than 26 carbon atoms per molecule and or wood sterols derived from non-saponifiable compounds contained in black liquor soaps or tall oil pitch useful for lowering serum cholesterol is disclosed in the

present invention. Food and pharmaceutical compositions containing these fatty alcohols or sterols or sterol esters are provided.

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Description

[0001] The present invention is related to food and pharmaceutical compositions containing fatty alcohols of 26 or less carbon atoms per molecule such as octadecanol, eicosanol, docosanol, tetracosanol or hexacosanol and or wood sterols useful for treating hypercholesterolemia in human beings.

[0002] Disorders of lipid metabolism especially harmful effects caused by high levels of serum cholesterol have been intensively investigated.

[0003] Cholesterol levels in blood over 200 mg/dl constitute the main risk factor of coronary diseases, the most frequent cause of death, principally in developed countries. However, the risk factor is not only related to high cholesterol level in blood, but also to different forms of total cholesterol. A high level of low-density lipoprotein or LDL cholesterol and very low-density lipoprotein or VLDL cholesterol in blood constitutes a problem because these lipoproteins are very likely to remain in the cardiovascular system causing the formation of plaques in the coronary arteries. Likewise, low levels of high-density lipoproteins or HDL cholesterol constitute an additional risk factor because they are useful in removing the form of cholesterol that blocks arteries. Therefore total cholesterol level and total cholesterol HDL cholesterol ratio must be considered for evaluating the risk of coronary diseases.

[0004] Many food and pharmaceutical compositions containing natural products or by-products that lower serum cholesterol are used for treating hypercholesterolemia. Among natural products recently disclosed for this end are the long chain aliphatic alcohols or fatty alcohols generally denominated policosanols. This fatty alcohols is found in vegetal waxes where they occur esterified with fatty acids. During the processing of vegetal matter, waxes are normally hydrolyzed which leads to mixtures comprising different fatty alcohols. The aliphatic chain of these alcohols may contain from 18 to 38 carbon atoms. It is thought that policosanols interfere with cholesterol synthesis in the liver.

[0005] US Patent No. 5,856,316 discloses a composition of policosanols useful for treating hypercholesterolemia and other metabolic disorders containing a mixture of aliphatic alcohols having from 24 to 34 carbon atoms per molecule which are obtained from sugarcane waxes.

[0006] US Patent No. 5,952,393 discloses a composition comprising mixtures of phytosterols and policosanols useful for lowering serum cholesterol. Phytosterols of the invention consist of a mixture of β -sitosterol, campesterol and stigmasterol obtained from vegetal oil meanwhile the policosanols, which comprise aliphatic alcohols having from 20 to 36 carbon atoms per molecule, derive from rice bran wax.

[0007] Table I shows composition and content of mixtures of policosanols disclosed in the state of art quoted, along with compositions of policosanols of the present invention also called "wood alcohols". Table I compares the fatty alcohol composition of sugarcane wax, rice bran wax disclosed in the state of art and that of "wood sterols" contained in either tall oil pitch or tall oil soap of the present invention.

Table I: Fatty alcohol or policosanol composition of sugarcane wax, rice bran wax and "wood alcohols"

Source	Wax alcohols		"Wood alcohols"	
Aliphatic alcohol	Sugarcane wax	Rice bran wax	Tall oil pitch	Tall oil soap
Octadecanol (C18)	--	--	--	1.0 – 10.0
Eicosanol (20)	--	--	1.0 – 5.0	5.0 – 25.0
Docosanol (22)	--	1.1 – 1.6	5.0 – 30.0	2.0 – 60.0
Tetracosanol (24)	0.5 – 1.0	9.7 – 14.0	20.0 – 60.0	20.0 – 50.0
Hexacosanol (26)	5.5 – 8.5	8.9 – 12.7	15.0 – 50.0	1.0 – 5.0
Heptacosanol (27)	2.0 – 3.5	--	--	--
Octacosanol (28)	60.0 – 70.0	16.9 – 24.3	--	--
Nonacosanol (29)	0.4 – 1.2	--	--	--
Triacontanol (30)	10.0 – 15.0	25.3 – 36.3	--	--
Dotriacontanol (32)	4.0 – 6.0	14.1 – 20.2	--	--
Tetracontanol (34)	0.4 – 2.0	6.7 – 9.6	--	--
Hexatriacontanol (36)	--	1.5 – 2.2	--	--

[0008] It is noticed that policosanols from sugarcane wax do not contain aliphatic alcohols with less than 24 carbon atoms per molecule and the alcohols with less than 24 carbon atoms per molecule made up less than 2% of total alcohol in policosanols of rice bran wax. In both compositions, fatty alcohols with 28 or more carbon atoms per molecule constitute over 70% of the total fatty alcohols, and that "wood alcohols" do not contain fatty alcohols with more than 26 carbon atoms per molecule.

[0009] On the basis of compositions of policosanols disclosed in the state of art for their serum cholesterol lowering effect, it might be expected that said effect of policosanols would be characterisitic only of aliphatic alcohols having more than 26 carbon atoms per molecule. However, it has been surprisingly discovered that "wood alcohols" comprising octadecanol (estearyl alcohol), eicosanol (arachidyl alcohol), docosanol (behenyl alcohol), tetracosanol (lignoceryl alcohol) and hexacosanol (ceryl alcohol), the "wood alcohols" of the present invention exhibit an important serum cholesterol lowering effect when are ingested orally in low dose either in food or pharmacological compositions. Mixtures of octadecanol, eicosanol, docosanol, tetracosanol or hexacosanol of the present invention having a mean composition shown in Table I are by-products of cellulose industry or by-products of tall oil distillation hereafter called "wood alcohols". These "wood alcohols" can be produced in high yield and purity by processes disclosed in Chilean patent applications 85/98 and 2026/99 and reproduced in Examples 1 and 2.

[0010] Free sterols or steryl esters are also efficient serum cholesterol lowering agents. It has been observed that when a mixture of "wood alcohols" with "wood sterols" or esterified "wood sterols" are used in food or pharmaceutical compositions, the hypocholesterolemic effect of the mixture is higher than the effect of either "wood alcohols" or "wood sterols" alone especially in lowering LDL cholesterol; that is there is surprising synergistic effect of the mixture on the reduction of the ratio total cholesterol/high density lipoprotein (HDL).

[0011] Processes for the production of "wood sterols" are disclosed as well in Chilean patent application 2026/99.

[0012] Therefore, an objective of the present invention is to provide food and pharmaceutical compositions for lowering serum cholesterol preferably in human beings, where the composition comprise long chain aliphatic alcohols having 26 or less carbon atoms per molecule.

[0013] A further objective of the present invention is to provide a method for lowering serum cholesterol preferably in human beings, by means of orally administering food or pharmaceutical compositions comprising long chain aliphatic alcohols having 26 or less carbon atoms per molecule. Daily dose of said compositions comprise 0.01 and 50 mg of "wood alcohols" per kilogram of body weight.

[0014] Food and pharmaceutical compositions useful for lowering serum cholesterol comprise "wood alcohols" or "wood alcohols" and either free or esterified "wood sterols". "Wood alcohols" can be produced according to processes disclosed in Chilean patent application N°85/98. "Wood sterols" comprising both sterols and stanols can be obtained according to processes disclosed in Chilean patent application N°2026/99.

[0015] In the present invention, the term "wood alcohols" stand for a mixture comprising octadecanol, eicosanol, docosanol, tetracosanol or hexacosanol. The term "wood sterols" stands for a mixture comprising saturated sterols or stanols and non-saturated sterols. Table II shows the average composition of "wood sterols". Likewise, the term "esterified wood sterols" refers to a mixture containing saturated or non-saturated sterols and esterified with fatty acids. The esterified wood sterols can be obtained by processes disclosed in Chilean patent application N°. 209/00.

Table II:

Average composition of "wood sterols"	
Sterol	% in weight
Beta-sitosterol	45 - 70
Beta-sitostanol	10 - 25
Campesterol	3 - 15
Campestanol	1 - 10
Stigmasterol	Less than 5

Food composition useful for lowering blood serum levels of cholesterol can be prepared by incorporating "wood alcohols" into fatty foods such as edible oil, butter, margarine, chocolate, milk or its by-products (ice cream, yogurt, cheese) or by incorporating "wood alcohols" into non fatty foods.

[0016] Ice cream containing "wood alcohols" or "wood sterols" or esterified "wood sterols" can be prepared according to procedures disclosed in the state of the art. Said alcohols or sterols can partly substitute the fatty matter employed in the elaboration of ice cream.

[0017] Pharmaceutical compositions useful for lowering serum cholesterol can be prepared by formulating compo-

sitions comprising "wood alcohols" or "wood alcohols" and "wood sterols" or esterified "wood sterols" as active components together with pharmaceutically acceptable vehicles such as excipients, binders, stabilizers, lubricants, preservatives or coating agents. According to the present invention, pharmaceutical compositions can be provided in the form of tablets, capsules, pills, syrup, suppositories, subcutaneous dispensers or dermal patches.

[0018] According to the above disclosure a composition for lowering serum cholesterol in human subjects comprises one or more component selected from the group consisting of octadecanol, eicosanol, docosanol, tetracosanol and hexacosanol, or one or more component selected from the group consisting of octadecanol, eicosanol, docosanol, tetracosanol and hexacosanol, and one or more component selected from the group consisting of beta-sitosterol, beta-sitosteryl ester of a fatty acid, beta-sitostanyl ester of a fatty acid, campesterol, campesteryl ester of a fatty acid, campestanol, campestanyl ester of a fatty acid, stigmasterol and stigmasteryl ester of a fatty acid; and a method for lowering serum cholesterol in human subjects comprises periodically administering to said humans said composition at a blood serum cholesterol lowering effective dose.

Examples:

Example 1: "Wood alcohols" from tall oil soap

[0019] 150 g of unsaponifiable matter of tall oil soap with 0.8% humidity was fed at the rate of 2 g/min into a shorth path distillation column, model KDL-4 UIC GmbH. The evaporator temperature was kept at 210°C, the temperature of the internal condenser was 65°C, and the pressure in the column was 0.2 mbar. 63.2 g of distillate or overhead product and 82.8 g of or bottom product were recovered. Then, 50 g of the distillate was dissolved in 500 g of methanol at 50°C. Upon cooling down de dissolution to 15 °C a precipitate was formed and this precipitate was recovered by filtration and washed with fresh methanol. The yield was 2.8 g of precipitate.

The total fatty alcohol content of the precipitate was 95 % in weight and its composition is shown in Table III.

Table III:

Composition of the precipitate of Example 1	
Fatty alcohol	% in weight
Octadecanol	4.0
Eicosanol	23.4
Docosanol	27.7
Tetracosanol	34.8
Hexacosanol	5.1
Heptacosanol	--
Octacosanol	--
Nonacosanol	--
Triacosanol	--
Dotriacontanol	--
Tetratriacontanol	--
Hexatriacontanol	--

The mixture of policosanols shown in Table III is an example of "wood alcohols" derived from black liquor soaps.

Example 2: "Wood alcohols" from tall oil pitch

[0020] A precipitate fom unsaponifiable matter from tall oil pitch was obtained as described in Example 1. The composition of the mixture containing 97.4 % in weigth of poliocasanols is shown in Table IV.

Table IV:

Composition of the precipitate of Example IV	
Fatty alcohol	% in weight
Octadecanol	--
Eicosanol	2.5
Docosanol	19.7
Tetracosanol	53.1
Hexacosanol	22.1
Heptacosanol	--
Octacosanol	--
Nonacosanol	--
Triacosanol	--
Dotriacontanol	--
Tetratriacontanol	--
Hexatriacontanol	--

[0021] The mixture of policosanol shown in Table IV is an example of "wood alcohols" derived from tall oil pitch.

[0022] "Wood alcohols" as shown in the previous examples, typically do not contain fatty alcohols or policosanols with more than 26 carbon atoms per molecule of fatty alcohol.

Example 3 : "Wood sterols" from tall oil pitch

[0023] 200 g of bottom product obtained by distilling unsaponifiable matter of tall oil pitch as described in Example 1 were dissolved at 60°C in 700 g of a heptanol/methanol/water mixture (3/0.1/0.1 v/v) and then cooled down to 20°C until a precipitate was formed which was filtered out, washed with methanol and dried. The composition of the precipitate is shown in Table V.

Table V:

Composition of the precipitate of Example 3	
Sterol	% in weight
Beta-sitosterol	68.4
Beta-sitostanol	21.8
Campesterol	6.1
Campestanol	1.1
Stigmasterol	Less than 1

The mixture of sterols shown in Table V is an example of "wood sterols" derived from tall oil pitch.

Example 4: Preparation of mayonnaise containing "wood alcohols" and esterified "wood sterols".

[0024] "Wood sterols" used in this example had the composition shown in Table V and "wood alcohols" used in this example had the composition shown in Table IV. "Wood sterols" were esterified with ethyl esters fatty acids of rapeseed oil at 80°C and 1 mbar in presence of 0.5% of sodium ethylate as described in Chilean patent application N°209/00. The composition of the mayonnaise is shown in Table VI.

Table VI:

Composition of mayonnaise of Example 4	
Ingredient	% in weight
Modified starch	2.86
Methylhydroxycellulose	1.18
Salt	0.75
Powdered mustard	0.62
Saccharine	0.19
Clove, garlic, onion, pepper	0.93
Anhydrous citric acid	0.50
Sodium citrate	0.16
Ascorbic acid	0.09
Sorbitol	0.75
Vinegar	2.00
Egg yolk	7.45
Vegetal oil	20.00
Esterified "wood sterols"	5.00
"Wood alcohols"	0.10
Water	57.42

30 Preparation:

[0025] "Wood sterols" used in this example had the composition shown in Table V and "wood alcohols" used in this example had the composition shown in Table IV.

35 [0026] 100 g of mayonnaise are prepared by mixing in a beaker water with the ingredients shown on the table excepting vegetal oil, egg yolk, esterified "wood sterols" and "wood alcohols", to form an aqueous solution. In a separate beaker 20 g of vegetal oil were heated to 80°C and "wood alcohols" were added to form a first homogeneous mixture. Next, esterified "wood sterols" were gradually added to the mixture to form a second homogeneous mixture which was let to cool to 40°C and then the egg yolk was added with mixing to form a third mixture. After reaching said third mixture room temperature, the aqueous solution was added to it gradually under homogeneizing conditions. A daily intake by an adult of about 20 of the mayonnaise of the example should be sufficient for significantly lowering blood serum cholesterol level.

Example 5 . Margarine containing "wood alcohols".

45 [0027] 250 g of table margarine were melted and heated to approximately 80°C, then 200 mg of "wood alcohols" of the composition shown in Table IV are mixed in forming a homogeneous mixture. When the mixture was cooled down to room temperature it formed a solid and readily spreadable product whose organoleptic characteristics do not differ from conventional margarine. The described process can be applied to any animal or vegetal fatty matter used as table product , e.g. butter, or as a baking product. A daily intake by an adult of about 20 of the margarine of the example should be sufficient for significantly lowering blood serum cholesterol level.

Example 6: Ice cream containing "wood alcohols" and "wood sterols" as non milk fats.

[0028] Ice cream of the composition shown in Table VII was prepared.

Table VII.

Composition of ice cream of Example 6	
Ingredient	% in weight
Water	62.00
Lactose	6.00
Sucrose	12.00
Sodium caseinate	0.70
"Wood alcohols"	0.02
"Wood sterols"	2.00
Hydrogenated vegetable oil	11.00
Powdered skimmed milk	4.90
Mono and diglycerides	0.50
Mineral salts	0.80
Colorant and flavoring agents	0.08

Preparation.

[0029] Lactose, sucrose, skimmed milk, mineral salts and sodium caseinate were dissolved at about 60°C in a beaker. In another beaker hydrogenated vegetable oil was melted and mixed with the "wood alcohols", "wood sterols" and mono and diglycerides. "Wood alcohols" and "wood sterols" had the same composition as those used in Example 4. Then, the content of the two beakers were vigorously mixed together at about 80 °C and the emulsion so formed were homogenized using an Eberbach 8017 laboratory homogenizer. The resulting mixture was whipped with air and then frozen. Ice cream density was about 620 g per liter and its appearance and organoleptic characteristics did not differ significantly from ice cream similarly prepared containing 12% of fatty matter but lacking "wood alcohols" or "wood sterols". A daily intake by an adult of about 50 g of the ice cream of the example should be sufficient for significantly lowering blood serum cholesterol level.

Example 7: Preparation of cooking oil containing "wood alcohols" and "wood sterols"

[0030] 97.4 g of sunflower oil were charged into a 250 ml flat bottom glass flask with 4 standard ground necks provided high shear mixer, nitrogen bleaching, followed by the gradual addition of 100 mg of "wood alcohols" and 2.5 g of "wood sterols" of the same composition as those used in Example 4 until a homogeneous mixture was obtained, which remained liquid at room temperature. Said mixture can be used as conventional cooking or salad dressing oil. A daily intake by an adult of about 20 g of oil of the example should be sufficient for significantly lowering blood serum cholesterol level.

Example 8: Reconstituted milk containing "wood alcohols".

[0031] 1.6 g of sodium salt of rapeseed oil fatty acids are dissolved in 1 liter of skimmed milk. Next, 30.4 g of cooking oil prepared as described in example 7 but containing 1 % in weight of "wood alcohols" are added dropwise to the milk under vigorous agitation using a high shear mixer. After addition of the oil, stirring is continued for 15 minutes more. At the end a reconstituted stable milk is obtained. A daily intake by an adult of about 100 ml of reconstituted milk of the example should be sufficient for significantly lowering blood serum cholesterol level.

Example 9: Beverage containing wood alcohols and esterified wood sterols.

[0032] Mixture C containing 92.5 g of rapeseed oil, 500 mg of "wood alcohols" and 7 g of "wood sterols" is prepared as described in Example 4. Next, mixtures A and B are prepared.

Mixture A	
Tap water	700.0 g
High fructose syrup	80.0 g
Sucrose	20.0 g
Citric acid	20.0 g
Sodium citrate	10.0 g
Sodium benzoate	4.9 g
Sodium sorbate	5.0 g
Aspartame	0.1 g

Mixture B	
Tap water	95.0 g
Guar gum	31.6 g
Titanium dioxide	0.5 g
Caramel (as colorant)	1.5 g
Tartrazine	1.0 g
Mixture C	30.4 g

[0033] Components of mixture B are vigorously mixed together to form an emulsion. Then mixture B is poured gradually and under vigorous stirring over 2 l of a mixture A, until reaching complete homogeneity. A slightly turbid beverage is obtained. A daily intake by an adult of about 200 ml of beverage of the example should be sufficient for significantly lowering blood serum cholesterol level.

Example 10: Preparation of tablets containing "wood alcohols"

[0034] 20 g of "wood alcohols" of the composition shown in Table IV are melted at approximately 55°C and vigorously mixed with 386 g of calcium phosphate used as filler. Once the mixture is cooled down at room temperature, it is thoroughly mixed with 24 g of estearic acid and 7 g of magnesium estearate as lubricants, 10 g of silicon dioxide as diluent and 50 g of cellulose as coating material. The amount of material prepared is used to make 1,000 tablets by compressing the resulting mixture in a conventional pill press. A daily intake by an adult of up to 4 tablets of the example should be sufficient for significantly lowering blood serum cholesterol level.

Example 11: Tablets containing "wood alcohols" and "wood sterols"

[0035] A composition of tablets which is made as described in Example 10 is the following:

Component	mg/tablet
"Wood alcohols"	20
"Esterified wood sterols"	480
Lactose	400
Calcium lactate	100
Magnesium estearate	10
Talc	10
Sucrose	10
Microcrystalline cellulose	70

[0036] "Wood sterols" used in this example had the composition shown in Table V and "wood alcohols" used in this example had the composition shown in Table IV. A daily intake by an adult of up to 4 tablets of the example should be sufficient for significantly lowering blood serum cholesterol level.

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Example 12: Effect of "wood alcohols" and estrified "wood sterols" in test animals

[0037] "Wood sterols" used in this example had the composition shown in Table V and "wood alcohols" used in this example had the composition shown in Table IV 30 Sprague Dawley male rats divided at random into five groups of six animals each are fed for ten days with the following diets:

Diet	Ingredients
C ₀	P
C ₁	P+C
C ₂	P + C + EE
C ₃	P + C + PC
C ₄	P + C + PC + EE

where

P : *Champion* pellets ground and mixed with 5% in weight of corn oil

C : 1% in weight of cholesterol Merck, 95 % purity

EE : 1% in weight of esterified "wood sterols"

PC : 1% in weight of "wood alcohols".

Percentages are relative to the mixture of ingredients.

[0038] Dietary treatment was individually applied and corporal weight and dietary consumption were measured. At the end of the feeding period, total cholesterol content (TC) in the liver and serum and LDL cholesterol in serum of each animal were measured. The following results were obtained.

Food	TC liver (mg/g)	Sample standard deviation	TC serum (mg/dl)	Sample standard deviation	LDL serum (mg/dl)	Sample standard deviation
C ₀	1.53	0.12	80.40	7.13	56.72	5.09
C ₁	2.82	0.19	96.80	7.80	71.26	8.34
C ₂	1.28	0.15	87.58	1.14	71.75	9.35
C ₃	2.90	0.10	82.17	4.30	48.03	3.88
C ₄	1.20	0.11	72.30	4.27	38.72	4.43

Statistics

[0039] Comparisons of pair of means were made by Duncan multiple range test and the results were:

[0040] Total cholesterol in liver:

Difference	Significance at 5%
C ₃ - C ₄	Significant
C ₃ - C ₂	Significant
C ₃ - C ₀	Significant
C ₃ - C ₁	Non-significant
C ₁ - C ₄	Significant
C ₁ - C ₂	Significant
C ₁ - C ₀	Significant

(continued)

Difference	Significance at 5%
$C_0 - C_4$	Significant
$C_0 - C_2$	Significant
$C_2 - C_4$	Non-significant

[0041] Total cholesterol in serum:

Difference	Significance at 5%
$C_1 - C_4$	Significant
$C_1 - C_0$	Significant
$C_1 - C_3$	Significant
$C_1 - C_2$	Significant
$C_2 - C_4$	Significant
$C_2 - C_0$	Non-significant
$C_2 - C_3$	Non-significant
$C_3 - C_4$	Significant
$C_3 - C_0$	Non-significant
$C_0 - C_4$	Non-significant

[0042] LDL cholesterol in serum:

Difference	Significance at 5%
$C_2 - C_4$	Significant
$C_2 - C_3$	Significant
$C_2 - C_0$	Significant
$C_2 - C_1$	Significant
$C_1 - C_4$	Non-significant
$C_1 - C_3$	Non-significant
$C_1 - C_0$	Non-significant
$C_0 - C_4$	Significant
$C_0 - C_3$	Significant
$C_3 - C_4$	Significant

Analysis of results indicates that a diet rich in cholesterol increases content of total cholesterol in liver, blood serum as well as LDL level in serum.

[0043] Presence of policosanols in diet does not compensate said increase in the liver but presence of esterified "wood sterols" does. It can be observed that decrease of cholesterol in the liver is lower with food C_4 than with food C_2 , although this difference is not significant. It can also be observed that there seems to be no correlation between cholesterol content in the liver and content of total cholesterol and LDL cholesterol in serum.

[0044] As expected, a diet rich in cholesterol increases total cholesterol in serum which is compensated by the presence of "wood alcohols" or esterified "wood sterols" in the diet. Likewise, the presence of one of these compounds in diet does not cause a significant difference in serum cholesterol with respect to a diet without supplementary cholesterol. However, it can be observed that simultaneous presence of "wood alcohols" and esterified "wood sterols" in a diet rich in cholesterol decrease significantly cholesterol levels with respect to diet without supplementary cholesterol evidencing some kind of synergism in their cholesterol lowering activities between both.

Effects of "wood alcohols" in decreasing serum LDL cholesterol are significant and it can be observed again a synergistic effect of "wood alcohols" and esterified "wood sterols" in the diet.

Example 13: Tests in human subjects

[0045] In a non-controlled experience, five male adults consumed margarine enriched with "wood alcohol"s prepared as described in Example 5 for six weeks. Portions of margarine daily consumed amounted to a daily intake between 20 and 30 mg of "wood alcohols". Lipid profiles, total cholesterol (TC), LDL cholesterol and HDL cholesterol (mg/dl) were the following:

Subject	Initial TC	Final TC	Initial LDL	Final LDL	Initial HDL	Final HDL
1	234	207	141	115	62	61
2	215	185	132	105	55	52
3	196	181	128	114	42	44
4	202	203	130	129	40	41
5	184	161	115	99	48	45
Average	206	187	129	112	49	48

Student's test for the pairwise comparison of the means indicate a significant decrease of total cholesterol with a confidence level of 95% and a significant decrease of LDL cholesterol with a confidence level of 90%.

Claims

1. A composition for lowering serum cholesterol in human subjects wherein the composition comprise one or more components selected from the group consisting of octadecanol, eicosanol, docosanol, tetracosanol or hexacosanol, or one or more components selected from the group consisting of octadecanol, eicosanol, docosanol, tetracosanol and hexacosanol, and one or more component selected from the group consisting of beta-sitosterol, beta-sitosteryl ester of a fatty acid, beta-sitostanyl ester of a fatty acid, campesterol, campesteryl ester of a fatty acid, campestanol, campestanyl ester of fatty acid, stigmasterol, and stigmasteryl ester of a fatty acid.
2. The composition according to claim 1 comprising one or more a food substances selected from the group consisting of edible oil, margarine, butter, salad dressing, milk and beverages.
3. The composition according to claim 1 comprising one or more pharmaceutically acceptable component.
4. The composition according to claim 3 wherein the pharmaceutically acceptable component comprise binders, lubricants, stabilizers, preservatives, diluents or coating agents.
5. A method for lowering serum cholesterol in human subjects wherein the method comprise periodically administering via oral to said humans an effective amount of a composition comprising one or more components selected from the group consisting of octadecanol, eicosanol, docosanol, tetracosanol and hexacosanol, or one or more components selected from the group consisting of octadecanol, eicosanol, docosanol, tetracosanol and hexacosanol, and one or more components selected from the group consisting of beta-sitosterol, beta-sitosteryl ester of a fatty acid, beta-sitostanyl ester of a fatty acid, campesterol, campesteryl ester of a fatty acid, campestanol, campestanyl ester of a fatty acid, stigmasterol and stigmasteryl ester of a fatty acid.
6. The method according to claim 5 wherein the composition comprise one or more a food substances selected from the group consisting of edible oil, margarine, butter, salad dressing, milk and beverages.
7. The composition according to claim 6 wherein the composition comprise one or more pharmaceutically acceptable components.
8. The method according to claim 7 wherein the pharmaceutically acceptable component comprise binders, lubricants, stabilizers, preservatives, diluents or coating agents.

9. The method according claims 5 to 8 wherein the effective amount of the composition comprise from 0.01 to 50 mg of octadecanol, eicosanol, docosanol, tetracosanol or hexacosanol, or 0.01 to 50 mg of octadecanol, eicosanol, docosanol, tetracosanol or hexacosanol, and from 1 to 200 mg of beta-sitosterol, beta-sitosteryl ester of a fatty acid, beta-sitostanol, beta sitostanyl ester of a fatty acid, campesterol, campesteryl ester of a fatty acid, campestanol, campestanyl ester of fatty acid, stigmasterol or stigmasteryl ester of a fatty acid, per kilogram of body weight.

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(11)

EP 1 177 729 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
25.09.2002 Bulletin 2002/39

(51) Int Cl.7: **A23L 1/30, A23L 1/23,
A61P 3/06**

(43) Date of publication A2:
06.02.2002 Bulletin 2002/06

(21) Application number: **01306414.2**

(22) Date of filing: **26.07.2001**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **03.08.2000 CL 20002187**

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(54) **Pharmaceutical and food compositions containing "wood alcohols" or "wood sterols" useful for lowering serum cholesterol**

(57) Dietary utilization of mixtures containing fatty alcohols of less than 26 carbon atoms per molecule and or wood sterols derived from non-saponifiable compounds contained in black liquor soaps or tall oil pitch useful for lowering serum cholesterol is disclosed in the

present invention. Food and pharmaceutical compositions containing these fatty alcohols or sterols or sterol esters are provided.

EP 1 177 729 A3



European Patent
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PARTIAL EUROPEAN SEARCH REPORT

Application Number

which under Rule 45 of the European Patent Convention EP 01 30 6414
shall be considered, for the purposes of subsequent
proceedings, as the European search report

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
P,X	WO 01 32031 A (PIRAKITIKULR PICHAI ;MENON VINOD P (US); MONSANTO CO (US); KINLEN) 10 May 2001 (2001-05-10) * the whole document *	1-9	A23L1/30 A23L1/23 A61P3/06
X	US 5 725 803 A (ENGEL WALTER) 10 March 1998 (1998-03-10) * abstract *	1,3,4	
D,X	US 4 391 732 A (LUNDMARK LARRY D) 5 July 1983 (1983-07-05) * column 3; example 3 *	1	
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			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			A21D A23L
INCOMPLETE SEARCH			
<p>The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.</p> <p>Claims searched completely :</p> <p>Claims searched incompletely :</p> <p>Claims not searched :</p> <p>Reason for the limitation of the search:</p> <p>see sheet C</p>			
Place of search		Date of completion of the search	Examiner
THE HAGUE		23 April 2002	Inceisa, L
CATEGORY OF CITED DOCUMENTS		<p>T : theory or principle underlying the invention</p> <p>E : earlier patent document, but published on, or after the filing date</p> <p>D : document cited in the application</p> <p>L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>	
<p>X : particularly relevant if taken alone</p> <p>Y : particularly relevant if combined with another document of the same category</p> <p>A : technological background</p> <p>O : non-written disclosure</p> <p>P : intermediate document</p>			

EPO FORM 1503 (3.82) (P4/C07)



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INCOMPLETE SEARCH
SHEET C

Application Number
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Although claims 5-9 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched incompletely:
5-9

Reason for the limitation of the search (non-patentable invention(s)):

Article 52 (4) EPC - Method for treatment of the human or animal body by therapy



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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- ☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):
- ☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

- ☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- ☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.
- ☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:
- ☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-9 partly



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LACK OF UNITY OF INVENTION
SHEET B

Application Number
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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-9 partly

Composition and method for lowering serum cholesterol wherein the composition comprises octadecanol or octadecanol and one or more components from the group consisting of following sterols or sterol-esters: Beta-sitosterol, beta-sitostanol, campesterol, campestanol, stigmasterol

2. Claims: 1-9 partly

Composition and method for lowering serum cholesterol wherein the composition comprises eicosanol or eicosanol and one or more components from the group consisting of following sterols or sterol-esters: Beta-sitosterol, beta-sitostanol, campesterol, campestanol, stigmasterol

3. Claims: 1-9 partly

Composition and method for lowering serum cholesterol wherein the composition comprises docosanol or docosanol and one or more components from the group consisting of following sterols or sterol-esters: Beta-sitosterol, beta-sitostanol, campesterol, campestanol, stigmasterol

4. Claims: 1-9 partly

Composition and method for lowering serum cholesterol wherein the composition comprises tetracosanol or tetracosanol and one or more components from the group consisting of following sterols or sterol-esters: Beta-sitosterol, beta-sitostanol, campesterol, campestanol, stigmasterol

5. Claims: 1-9 partly

Composition and method for lowering serum cholesterol wherein the composition comprises hexacosanol or hexacosanol and one or more components from the group consisting of following sterols or sterol-esters: Beta-sitosterol, beta-sitostanol, campesterol, campestanol, stigmasterol

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 01 30 6414

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
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23-04-2002

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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